DETAILED ACTION

Election/Restrictions

During a telephone conversation with attorney Robert Gamson on 17 December 2008 a provisional election was made with traverse to prosecute the invention of Group I, claims 27-64 and 81-119. Affirmation of this election must be made by applicant in replying to this Office action. Claims 65-74 and 122 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

It is noted that a written restriction requirement was mailed on 19 December 2008. The restriction requirement was actually written prior to the mail date but it was not mailed until a few days later, wherein Mr. Gamson's subsequent telephonic election came prior to the mail date. Therefore, this Office action incorporates by reference the entire content of the written restriction requirement but applicant's requirement to file a written election response is hereby waived because applicant responded to the telephone restriction practice before the mail date of the written restriction requirement.

Status of the Claims

Claims 27-64 and 81-119 are examined herein on the merits for patentability. No claim is allowed at this time.

Claim Objections

1. Claims 46 and 85 are objected to because of the following informalities: the claims recite ratios that include 6;4. However, it is believed by the examiner that Applicants intended to state the ratio 6:4. Appropriate correction is required.

2. Claim 104 is objected to because of the following informalities: the claim does not end with a period. Each claim begins with a capital letter and ends with a period. Appropriate correction is required.

3. Claims 85 and 91 are objected to because of the following informalities: the 3rd line of both claims reads "in ratio of". However, the claims should read - -in a ratio of- -. Appropriate correction is required.

Specification

1. The amendment filed 04 August 2005 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: new paragraphs [00016.1]-[00016.3], [00017.1], the concentration ranges disclosed in newly amended paragraph [00022]; new paragraphs [00022.1]-[00022.12]; and the concentration ranges disclosed in newly amended paragraphs [00036] and [00052]-[00055]. The examiner directs attention to MPEP 2163(I)(B) wherein it states, "subgenus range was not supported by generic disclosure and specific example within the subgenus range", and

"a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads". In the absence of evidence to the contrary, the newly added or amended paragraphs do not find support in the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 27-64 and 81-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims contain percentage ranges of hormones that were not described in the original disclosure. In particular, the original disclosure does not provide support for about 3.5 to about 80% hormone; about 10.1 to about 25.1% hormone; about 25.1 to about 80% hormone; about 3.5 to about 100% estriol, estradiol, or combinations thereof; about 5.1 to about 100% estriol, estradiol, or combinations thereof; about 3.5 to about 100% estriol, estradiol, estrone, or combinations thereof; about 5.1 to about 100% estriol, estradiol, estrone, or combinations thereof; about 6.4 to about 80% testosterone; about 10.1 to about 80% testosterone; about 25.1 to about 80% testosterone; about 10.1 to about

90% progesterone; about 20.1 to about 90% progesterone; and about 6.1 to about 100% estriol, estradiol, estrone, or combinations thereof.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 27-64 and 81-119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, claims 27-64 and 81-119 recited a percent of hormone and solvent. However, it is unclear whether the percentage of each component is percent by weight, volume, etc. For the purposes of examination, the claims are construed as percent by weight.

2. Claim 34 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the claim states that the composition is in a powder form. However, claim 34 is dependent from claim 27 which requires about 20 to about 96.5% of at least one solvent. The instant specification defines solvent as a liquid ([00056]). Therefore, it is unclear how the composition can have about 20 to about 96.5% solvent and still be a powder.

3. Claim 91 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the claim states that the at least one hormone is a combination of estriol and estradiol in ratio of 5:4:1, 6:3:1, 7:2:1 or 8:1:1. However, the ratios indicate three ingredients, and it is unclear what the third ingredient is.

4. Claim 94 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, it is unclear what compounds constitute synergists. Synergy between two or more compounds is unpredictable, and therefore it is unclear which compounds will behave synergistically with the hormone and solvent composition.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 27, 30-32, 35-36, 39, 95 and 110 are rejected under 35 U.S.C. 102(b) as being anticipated by Taylor et al. (US 2,856,329).

Taylor et al. disclose a composition comprising 5 wt.% testosterone in a vehicle consisting of 15 wt.% propylene glycol, 5 wt.% benzyl alcohol and 80wt.% PEG 300 (Example 1).

Taylor et al. further disclose a composition comprising 5 wt.% testosterone in a vehicle consisting of 10 wt.% benzyl alcohol and 90 wt.% PEG 300 (Example 2).

Taylor et al. further disclose a composition comprising 2.5 wt.% testosterone in a vehicle consisting of 0.5 wt.% chlorobutanol and 99.5 wt.% PEG 300 (Example 3).

Taylor et al. further disclose a composition comprising 2.5 wt.% testosterone in a vehicle consisting of 50 wt.% propylene glycol and 50 wt.% PEG 300 (Example 4).

Taylor et al. further disclose a composition comprising 5 wt.% progesterone in a vehicle consisting of 45 wt.% propylene glycol, 15 wt.% benzyl alcohol, 35 wt.% PEG 300, and 5 wt.% acetic acid (Example 5).

Taylor et al. further disclose a composition comprising 5 wt.% progesterone in a vehicle consisting of 10 wt.% benzyl alcohol and 90 wt.% PEG 300 (Example 6).

Taylor et al. further disclose a composition comprising 0.2 wt.% estrogen in a vehicle consisting of 5 wt.% benzyl alcohol and 95 wt.% PEG 300 (Example 7).

Taylor et al. further disclose a composition comprising 0.5 wt.% estrone in a vehicle consisting of 5 wt.% benzyl alcohol and 95 wt.% PEG 300 (Example 8).

Taylor et al. further disclose a composition comprising 0.12 wt.% estradiol, 2.5 wt.% testosterone, and 2.5 wt.% progesterone in a vehicle consisting of 10 wt.% benzyl alcohol and 90 wt.% PEG 300 (Example 9).

Taylor et al. further disclose a composition comprising 2.5 wt.% testosterone and 0.2 wt.% estrone in a vehicle consisting of 5 wt.% benzyl alcohol and 95 wt.% PEG 300 (Example 10).

2. Claims 27, 28, 30-33, 35, 36, 39-44, 47-51, 87, 92, 93, 101, 102, 104, 110 and 112-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Chiang et al. (WO 90/11064).

Chiang et al. disclose compositions comprising up to 15 wt.% drug (i.e., 5 wt.% estrogen and 10 wt.% progestrogen) and 5-40 wt.% enhancer composition (i.e., 80:20 v/v Transcutol/PGML (diethylene glycol monoethylether/propylene glycol monolaurate)) and up to 4 wt.% silicone oil (pg. 13, ln. 1-10). Chiang et al. further disclose examples wherein the compositions comprise 5 wt.% estradiol and 14 or 20 wt.% enhancer (Transcutol/PGML) and 81 or 75 wt.% silicone oil (pg. 24, Example 6, Table 6).

Chiang et al. further disclose that the composition may in addition include one or more selected carriers or excipients, and various agents and ingredients commonly employed in dermatological ointments and lotions, such as fragrances, opacifiers, preservatives, anti-oxidants, gelling agents, perfumes, thickening agents, stabilizers, surfactants, emollients, coloring agents, and the like (pg. 11, ln. 10-17).

3. Claims 27-32, 35, 36, 39, 54-59, 93, 110, 111, 116 and 117 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen '148 (WO 97/24148).

Chen '148 disclose compositions comprising from 54.6 to 156.7 mg/ml testosterone in a solvent system such as oleic acid:methyl laurate:propylene glycol (PG) (10:45:45), oleic acid:methyl laurate:1,2-butanediol (10:45:45), oleic acid:PG:1,2-butanediol (10:45:45), oleic acid:methyl laurate:transcutol (diethylene glycol monoethylether) (10:45:45), oleyl alcohol:methyl laurate:PG (10:45:45), oleyl alcohol:propylene glycol monolaurate (PGML):1,2-butanediol (10:45:45), benzyl alcohol:PGML:1,2-butanediol (10:45:45), and PGML (Table 2).

Chen '148 further disclose compositions comprising 80.9 to 241.2 mg/ml testosterone in a solvent system such as oleyl alcohol:PGML:1,2-butanediol (10:45:45), oleyl alcohol:PGML:1,2-butanediol (45:40:15), oleyl alcohol:PGML:1,2-butanediol (40:30:30), lauric acid:methyl laurate:1,2-butanediol (20:40:40), lauric acid:PG:1,2-butanediol (20:40:40), oleyl alcohol:PGML:PG (10:45:45), benzyl alcohol:methyl decanoate:1,2-butanediol (20:40:40), lauryl alcohol:methyl laurate:1,2-butanediol (20:40:40), and lauryl alcohol:methyl laurate:PG (20:40:40) (Table 3).

4. Claims 27, 30-32, 35-39, 94, 96, 110 and 111 are rejected under 35 U.S.C. 102(b) as being anticipated by Carrara et al. (WO 02/11768).

Carrara et al. disclose a gel composition comprising in weight percent 3.5% testosterone, 2.00% lauryl alcohol, 5.01% transcutol (diethylene glycol monoethylether),

5.93% propylene glycol, 49.22% ethyl alcohol, 32.73% water, 1.2% carbomer, 0.35% triethanolamine, and 0.06% disodium EDTA (pg. 18, Example 5).

5. Claims 27, 30-32, 35, 36, 39, 92-100, 110 and 111 are rejected under 35 U.S.C. 102(b) as being anticipated by Patel et al. (US 6,248,363).

Patel et al. disclose a pharmaceutical composition comprising 8.6 wt.% progesterone, 22.9 wt.% solulan C-24, 5.7 wt.% distilled monoglycerides, 5.7 wt.% deoxycholic acid, and 57.1 wt.% non-pareil seed (Example 3). Patel et al. further disclose that other additives conventionally used in pharmaceutical compositions can be included, such as antioxidants, bufferants, chelating agents, colorants, diluents or fillers (i.e., lactose, talc, starch, cellulosics), disintegrants (i.e., starch, clays, gums, cellulose, alginates, PVP, microcrystalline cellulose), plasticizers, preservatives, thickeners, etc. (col. 39, ln. 10 - col. 40, ln. 60).

6. Claims 27, 28, 30-32, 35, 36, 39, 60, 62-64, 92-100, 110, 111, 118 and 119 are rejected under 35 U.S.C. 102(e) as being anticipated by Chen '297 (US 2003/007297).

Chen '297 disclose a pharmaceutical suspension formulation comprising up to about 19 wt.% progesterone or a mixture of progesterone and 2 wt.% estradiol, wherein the hormones are dispersed in a solvent system mixture comprising components selected from propylene glycol monocaprylate, PEG 35 castor oil, PEG 3350, α-tocopherol, vitamin E TPGS, PEG 6 corn oil, PG, glyceryl tricaprylate/caprate, polysorbate 80, glyceryl monolinoleate, PEG 40 hydrogenated castor oil, lactose, PEG

400, and Tween 80 (Examples 37-47). Chen '297 further disclose that the compositions further comprise at least one pharmaceutically acceptable additive, including a stabilizing agent, an antioxidant, a bufferant, a preservative, a chelating agent, and a colorant (claims 25 and 95).

7. Claims 27, 30-32, 34-36, 40-43, 45-50, 81-89, 93 and 110-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Lachnit-Fixson et al. (US 4,076,811).

Lachnit-Fixson et al. disclose compositions comprising a combination of estriol and estradiol in a ratio of 2:1, 4:1 and 8:1, wherein the estrogens are present at 3.75, 6.25, and 5.625 wt.% in lactose, corn starch, PVP 25, and talc, and optionally methylparaben and propylparaben (Examples 1-3, 1st Phase prior to supplementing with customary sugar).

8. Claims 27, 28, 30-36, 54, 55, 57-64, 100, 110, 111 and 116-119 are rejected under 35 U.S.C. 102(b) as being anticipated by Rudel (US 3,828,106).

Rudel discloses a composition comprising 0.93 g progesterone, 2.17 g cholesterol acetate, and 3.1 g lactose (i.e., 15 wt.% progesterone); and a composition comprising 0.93 g progesterone and 3.1 g lactose (i.e., 23.1 wt.% progesterone) (Example I). Rudel further discloses a composition comprising 1.2 g testosterone, 1.2 g cholesterol acetate, and 6 g lactose (i.e., 14.3 wt.% testosterone); and a composition comprising 1.2 g testosterone and 6 g lactose (i.e., 16.7 wt.% testosterone) (Example III). Rudel further discloses a composition comprising 48 mg progesterone and

cholesterol acetate, PVP, lactose, sucrose, sodium lauryl sulfate, magnesium stearate, and potato starch to a total of 528.5 mg (i.e., 9.1 wt.% progesterone) (Example VII).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 52, 53, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lachnit-Fixson et al. (US 4,076,811) in view of Muni (US 6,708,822).

Applicant's claims

Applicants claim a concentrated hormone pharmaceutical composition comprising about 3.5% to about 100% of at least one hormone, wherein said hormone is a combination of estriol, estradiol, and estrone in a ratio of 5:4:1, 6:3:1, 7:2:1 or 8:1:1.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Lachnit-Fixson et al. are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Lachnit-Fixson et al. do not teach the hormone compositions comprising a combination of estriol, estradiol and estrone in a ratio of 5:4:1, 6:3:1, 7:2:1 or 8:1:1, as instantly claimed. However, Muni teaches that there are many types and forms of hormone replacement therapy available to aging women. Typically, these compounded formulations comprise a combination of one or more estrogens and one progesterone. The importance of individualized therapy and the physician-pharmacist-patient relationship in providing optimal HRT is well documented. Rather than prescribing a very limited number of FDA approved HRT products, physicians are choosing and selecting various natural hormone combinations for post-menopausal women. Based upon family history and present health of a patient, a 30 day supply of Triest (i.e., three estrogen combination) or Biest (i.e., two estrogen combination) regimen with or without progesterone is commonly prescribed. Triest includes a mixture of estriol, estradiol, and estrone while Biest contains estriol and estradiol. Pre-weighed mixtures of these natural hormones which are all commercially available and FDA accepted, along with pre-weighed diluent (e.g., lactose) would easily be supplied in a typical 30-day unit of use kit. See col. 7, ln. 1-20. Muni further teaches a specific example comprising an 8:1:1 ratio of estriol, estradiol and estrone (Example 7).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to use a two or three estrogen combination in the composition of Lachnit-Fixson et al. for hormone replacement therapy, wherein the two estrogen combination comprises estriol and estradiol and the three estrogen combination comprises estriol, estradiol and estrone, as reasonably taught by Muni.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

2. Claims 103 and 105-109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiang et al. (WO 90/11064) and Chen '297 (US 2003/007297).

Applicant's claims

Applicants claim the hormone compositions according to claims 44, 51, 59 and 64, wherein said coloring agent provides a distinct color profile and is red, blue or yellow.

Determination of the scope and content of the prior art

(MPEP 2141.01)

The teachings of Chiang et al. and Chen '297 are discussed above and incorporated herein by reference.

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Chiang et al. and Chen '297 do not specifically teach their coloring agents to be red, blue or yellow. However, the desired color of the coloring agent is well within the purview of the skilled artisan.

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to add whichever pharmaceutically acceptable coloring agent was desired, such as red, yellow or blue, to the compositions of Chiang et al. and Chen '297.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is 571-272-9924. The examiner can normally be reached on 8:30 AM to 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616